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The Art and Science of Diagnosing and Managing Drug-induced Liver Injury in 2015 and Beyond

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Drug-induced liver injury (DILI) remains a leading reason why new compounds are dropped from further study or are the subject of product warnings and regulatory actions. Hy's Law of drug-induced hepatocellular jaundice causing a case-fatality rate or need for transplant of 10% or higher has been validated in several large national registries, including the ongoing, prospective U.S. Drug-Induced Liver Injury Network. It serves as the basis for stopping rules in clinical trials and in clinical practice. Because DILI can mimic all known causes of acute and chronic liver disease, establishing causality can be difficult. Histopathologic findings are often nonspecific and rarely, if ever, considered pathognomonic. A daily drug dose >50–100 mg is more likely to be hepatotoxic than does <10 mg, especially if the compound is highly lipophilic or undergoes extensive hepatic metabolism. The quest for a predictive biomarker to replace alanine aminotransferase is ongoing. Markers of necrosis and apoptosis such as microRNA-122 and keratin 18 may prove useful in identifying patients at risk for severe injury when they initially present with a suspected acetaminophen overdose. Although a number of drugs causing idiosyncratic DILI have HLA associations that may allow for pre-prescription testing to prevent hepatotoxicity, the cost and relatively low frequency of injury among affected patients limit the current usefulness of such genome-wide association studies. Alanine aminotransferase monitoring is often recommended but has rarely been shown to be an effective method to prevent serious DILI. Guidelines on the diagnosis and management of DILI have recently been published, although specific therapies remain limited. The LiverTox Web site has been introduced as an interactive online virtual textbook that makes the latest information on more than 650 agents available to clinicians, regulators, and drug developers alike.

Keywords: Drug-induced Liver Injury; DILI; Hepatotoxicity.

Art is science made clear

Wilson Mizner, 1836–1933

The pace of discovery for drug-induced liver injury (DILI) is at an all-time high. To illustrate just how fast the field is growing, one needs only to look at the number of new monographs, new editions of textbooks, single-topic conferences, and workshops specifically dedicated to DILI that continue to appear.[1–5] The explosion of publications relating to DILI is reflected in the more than 1500 citations in 2014 alone,[6] with >6000 found just under the specific search heading of "drug-induced liver injury" in PubMed in the past 5 years (2010 through 2014), a figure nearly equaling the number of articles on DILI found in the preceding decade (2000–2009).

Because of this large amount of new information, the thrust of this review will be limited largely to the key advances in the clinical diagnosis and management of idiosyncratic DILI (iDILI) during the past decade. In keeping with the theme of this special issue, an attempt will be made to describe the current state of the art of DILI balanced against new scientific findings, offering commentary on the areas of controversy that still remain and venturing beyond the current guidelines where it seems appropriate.

History of Drug-induced Liver Injury

The identification of several prototypical hepatotoxins, such as iproniazid, cinchophen, and sulfonamides, paved the way for the clinical and histologic descriptions of the numerous agents that followed after World War II.[7] Hans Popper[8] was fond of saying that DILI represented a "penalty for progress," referring to the agents from this early era, such as halothane, isoniazid (INH), carbamazepine, phenytoin, and alpha methyldopa. Nearly 1000 drugs were listed as possible causes of hepatic injury by the mid-1980s.[9] The seminal observations of Zimmerman[7] did much to define the field for much of the latter half of the 20th century, providing us with many of the diagnostic, pathophysiologic, and mechanistic principles that are still in use today. However, DILI remains a significant diagnostic challenge,

Abbreviations used in this paper: **ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; DI-ALF, drug-induced acute liver failure; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; FDA, Food and Drug Administration; HDS, herbal compounds and dietary supplements; iDILI, idiosyncratic drug-induced liver injury; INH, isoniazid; LAE, liver-associated enzyme; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.**

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because drugs can imitate all known causes of acute and chronic hepatic diseases[10] and act via multiple mechanisms of injury.[11–14]

Although severe DILI is a relatively rare clinical event, drugs have been the leading cause of acute liver failure (ALF) in the United States and other Westernized countries for several decades, with acetaminophen being responsible for 40%–50% of the cases and other drugs (including herbal compounds and dietary supplements [HDS]) being responsible for 11%–12%, a percentage equal to the frequency of ALF from acute viral hepatitis and greater than that seen with all other individually identified causes.[15,16] The prognosis for these patients with iDILI is often very poor, with a high case-fatality rate without urgent liver transplantation.[15,16] As a result, the concern for acute iDILI progressing to ALF has kept drug-induced hepatotoxicity a perennial target of regulatory actions and the ongoing focus of both pre-approval as well as post-marketing drug development safety efforts.[6,17–22]

The potential for a new chemical entity to cause serious liver injury has been among the leading reasons why novel compounds are halted in the early phases of testing, are not approved for use, or have been withdrawn in the post-marketing setting.[17,21,23] Because of the significant time and expense involved in bringing an innovative drug to market, it should not be surprising that substantial effort is aimed at identifying potentially program-ending toxicities as early as possible in the drug development process.[17] In silico modeling,[24] structural alerts,[25] and other preclinical methodologies are routinely used to avoid bringing forward molecules that are potentially hepatotoxic.[26–31] However, because not all compounds can be guaranteed to be free of liver injury in the preclinical stages, the past decade has also seen enormous strides made in the field of regulatory science to identify DILI in the clinical trial and post-approval phases of development, all directed at reducing the risk of severe hepatotoxicity in the population at large.[18–20] The introduction of the Evaluation of Drug-Induced Serious Hepatotoxicity plot,[32] the Rule-of-Two,[33,34] FDA Adverse Event Reporting System,[35] the Sentinel projects,[36] and Liver Toxicity Knowledge Base[37] has provided more powerful tools by which DILI can be detected and predicted. These advances in regulatory science parallel the many discoveries being made at the bedside, such as the description of new hepatotoxins such as ipilimumab,[38,39] dronedarone,[40] and tolvaptan,[22,41] updates of known hepatotoxins including telithromycin,[42] duloxetine,[43] fluoroquinolones,[44] statins,[45] azithromycin,[46] and tyrosine kinase inhibitors[47] among others.[6] In addition, enormous strides have been made in the exploration of novel mechanisms of injury,[12–14,31,48–53] the identification of risk factors and predictors of injury,[54–62] the refinement of causality assessment tools,[63–65] and new strategies to treat hepatotoxicity.[66–72]

Recently, the first guidelines on the diagnosis and management of DILI were offered by the Practice Parameters Committee of the American College of Gastroenterology,[73] which provide important summary statements and practical advice regarding all aspects of iDILI (Table 1). Much of the recent progress in defining updated clinical signatures, determining genetic risk factors and other circumstances of exposure, establishing causality, uncovering pnjuryotential biomarkers, etc, also parallels the establishment of the U.S. Drug-Induced Liver I Network (DILIN) in 2004.[74,75] The observations, associations, and other clinical discoveries that have been made from this prospective study during the past decade have helped to answer many questions regarding the natural history and prognosis of iDILI. The database currently contains >1200 patients with acute non-acetaminophen DILI attributable to nearly 200 different agents (including HDS).[76,77]

In addition to the data generated by the U.S. DILIN and other national registries during the past decade,[78–84] the recently launched LiverTox Web site (livertox.nih.gov) overseen by the National Institutes of Health and National Library of Medicine[85] provides the most

Table 1. Summary of American College of Gastroenterology DILI Guidelines

I. Elements necessary for a diagnostic evaluation of DILI
- Known duration of exposure
- Concomitant medications and diseases
- Response to dechallenge (and rechallenge if performed)
- Presence or absence of symptoms, rash, eosinophilia
- Performing sufficient exclusionary tests (viral serology, imaging, etc) to reflect the injury pattern and acuteness of liver function tests (eg, acute viral serology for A, B, and C and autoimmune hepatitis when presenting with acute hepatocellular injury; routine testing for hepatitis E virus not recommended because of the problems with current commercial assays; Epstein-Barr virus, cytomegalovirus, and other viral serology if lymphadenopathy, atypical lymphocytosis present)
- Sufficient time to determine clinical outcome—did the event resolve or become chronic?

II. Use of liver biopsy
- Often not required if the acute injury resolves
- Helpful in confirming clinical suspicion of DILI but rarely pathognomonic
- Useful to differentiate between DI-autoimmune hepatitis and idiopathic autoimmune hepatitis
- Useful to rule out underlying chronic viral hepatitis, nonalcoholic fatty liver disease, alcoholic liver disease, or other CLD
- Used to exclude DILI where re-exposure or ongoing use of an agent is expected

III. Rechallenge: generally best avoided, unless there is no alternative treatment

IV. Use of Causality Assessment Methods
- RUCAM is best considered an adjunct to expert opinion (it should not be the sole diagnostic method)
- Consensus opinion
- Expert consultation
- For patients with chronic viral hepatitis, DILI requires a high index of suspicion, knowledge of a stable clinical course before the new medication, and monitoring of viral loads to rule out flares of the underlying disease
- Assigning causality to HDS products can be especially difficult; requires knowledge of all ingredients and their purity

comprehensive, up-to-date, and interactive resource on more than 650 agents. Since its inception, millions of searches have been conducted on its contents, with projections that it will continue to expand in its role as the most up-to-date virtual textbook.

Although not a specific focus of this review, current research efforts into the mechanisms of DILI are being directed at the role of the intrinsic immune system,[86–88] mitochondrial injury,[48–50] the bile salt excretory pump,[31,89,90] as well as using the fields of metabolomics, transcriptomics, proteomics, etc.[91–96] For certain agents such as INH, the long-held mechanisms of injury are being redefined.[49,52] Although such efforts have brought us closer to understanding why DILI occurs, gaps in our knowledge base still remain.[2,4,17] Although pharmacogenomics is being actively pursued in an effort to uncover genetic risk factors predicting susceptibility to DILI,[54,55,97,98] how best to incorporate such new information into clinical practice and how to define its clinical utility remain to be determined.[99–104] To help arrive at these answers, workshops, conferences, and international consortia dedicated to DILI are actively attempting to bring clarity to the clinical and regulatory questions that remain. Through their collective efforts during the past 15 years, members of the Food and Drug Administration (FDA), academia, and industry have collaborated to collect and share resources on a global scale to better understand and predict hepatotoxicity.[4,5,17,20,105–110]

Epidemiology of Drug-induced Liver Injury

Because of its wide spectrum of clinical presentations and histologic manifestations that can be mimicked by any number of other hepatic disorders, DILI can be difficult to distinguish from other causes. Several studies illustrate that is both under-recognized and under-reported.[111–114] Aithal et al[111] found that about 50% of suspected DILI cases were actually caused by other common disorders when assessed by experts. In France, Sgro et al[112] found that DILI was being underreported by a factor of 16 when based on spontaneous reports, compared with when clinicians were properly trained to identify DILI cases.

Because acute DILI is, in fact, relatively rare, it should not be surprising that the exact incidence from individual agents, as well as from all causes, has been difficult to ascertain.[10,114] The most recent estimate of non-acetaminophen–related DILI comes from Iceland, with an incidence of 19.1 per 100,000 inhabitants,[82] which is similar to the incidence of 13.9 per 100,000 estimated by Sgro et al[112] a decade earlier. Estimates of DILI among hospitalized patients suggest that it is a very rare cause for admission (Table 2).[113,115,116]

It is thought that about 2000 cases of ALF occur annually in the United States, about half of which are due to DILI.[15,16] Most of these drug cases are due to acetaminophen toxicity (40% overall), with all non-acetaminophen cases representing about 11% (Table 3).[15,16] Although many clinicians will likely not have dealt with an individual case of drug-induced ALF (DI-ALF), defined as the abrupt onset of coagulopathy and encephalopathy in a patient without known liver disease, they will certainly be familiar with less severe DILI in the form of elevated liver-associated biochemistries, specifically aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]). Most of these patients will be asymptomatic, and it is likely that many thousands of cases occur but are either not recognized as DILI or go unreported.

Despite the potential for DI-ALF among the thousands of new chemical entities that initially undergo development, DILI was responsible for only 11 of 77 drug withdrawals from more than 6000 compounds during a 32-year period.[118] In subsequent years, other drugs have received warnings about hepatotoxicity, and some have had their indications restricted because of the risk of DILI (eg, trovafloxacin,[119] telithromycin[42]). Importantly, however, no approved prescription drug has been removed from the market for hepatotoxicity since the late 1990s[20]; the last withdrawals for DI-ALF were bromfenac[120] and troglitazone.[121] There have been relatively few drugs approved outside of the United States that failed to be approved in the United States because of hepatotoxicity,[17,23,122] although recent

Table 2. Incidence of DILI in Recent Studies

Author	Year	Location	Incidence
Sgro[112]	2003	France	13.9 cases per 100,000
Galan[117]	2005	U.S. tertiary referral	33% of patients presenting with acute hepatitis (0.8% of all consults)
Meier[113]	2005	Switzerland	1.4% of inpatients, from among more than 4200 admissions
Andrade[78]	2005	Spain	34.2 per 1,000,000 inhabitants/y 16.6 per 1,000,000 inhabitants/y serious life-threatening
Vuppalanchi[115]	2007	Hospitals in Indiana	<4% of cases with new onset jaundice (3% from acetaminophen, 0.7% from iDILI)
Carey[116]	2008	Mayo Clinic, Scottsdale	0.048% of 83,000 hospital admissions 1998–2006 (2/3 due to acetaminophen) (0.0156% representing iDILI)
Devarbhavi[80]	2010	Bangalore, India	2.46% of all hepatobiliary disease admissions 1997–2008 (58% due to antituberculosis DILI)
Suk[83]	2012	Korea	12 per 100,000 (70% herbal and folk remedies)
Bjornsson[82]	2013	Iceland	19.1 cases per 100,000

Table 3. Causes of ALF and Specific Drug-induced Causes in the U.S. Acute Liver Failure Study Group

2000 cases of ALF in USALFSG[15] Cause of ALF, no. of cases (%)	133 Cases of iDILI[16] Drug class, no. of cases (%)
Acetaminophen, 916 (45.8)	Anti-tuberculosis drugs, 25 (18.8)
Idiosyncratic DILI, 220 (11)	Non-sulfa antibiotics, 19 (14.3)
Hepatitis B, 142 (7.1)	Sulfonamides, 12 (9.0)
Hepatitis A, 36 (1.8)	Antifungals, 6 (4.5)
Autoimmune, 137 (6.8)	HDS, 14 (10.5)
Ischemic, 112 (5.6)	Antiepileptics, 11 (8.3)
Wilson disease, 25 (1.25)	Psychotropics, 4 (3.0)
Budd-Chiari, 15 (0.75)	Antimetabolics, 11 (8.3)
Pregnancy, 18 (0.09)	Nonsteroidal anti-inflammatory drugs, 7 (5.3)
Other, 134 (6.7)	Statins, 6 (4.5)
Indeterminant, 245 (12.25)	Biologics 4 (3.0)
	Others, 8 (6.0)

examples include ximelagatran[123,124] and lumiracoxib[125] (Table 4).

Hepatotoxicity due to HDS is being increasingly recognized and reported.[77,126–130] The DILIN registry currently lists HDS as causal in 16% of cases, second only to antimicrobials as the most common reason for all-cause DILI[76] (Table 5). Similarly, HDS is a significant cause of DI-ALF.[16] The increasing use of HDS, especially among patients with chronic liver disease (CLD),[126,127] has also been associated with an increase in safety alerts issued by the FDA as well as foreign regulatory bodies for several products,[6,77,128] most recently weight loss and muscle building compounds (eg, Herbalife,[131] OxyELITE Pro[132]). Significantly higher proportions of patients with DILI are due to HDS from series in Asia where complementary and alternative medicines represent a higher percentage of therapeutic options[83,133,134] (Table 5).

Although nearly 1000 drugs and chemicals have been described as being hepatotoxic during the past century,[7,9,85] most global registries list relatively few drugs as the cause of the majority of instances of DILI, many of which are well-known hepatotoxins. For example, in the latest DILIN registry of nearly 900 patients,[76] out of 190 agents, the top 5 accounted for 27% and the top 10 for more than one-third of all cases, indicating that most drugs causing DILI do so in relatively small numbers (Supplementary Table 1). A similar situation is seen in the United States Acute Liver Failure Study Group, where INH is the leading cause after acetaminophen[15,16] (Table 3). In India, where acetaminophen use is rare, antituberculous agents lead the list of severe and often fatal DILI.[80]

Recognizing Drug-induced Liver Injury

DILI has been traditionally divided into 3 main biochemical injury patterns (hepatocellular, cholestatic, and mixed) on the basis of the ratio of ALT to alkaline phosphatase (R value)[135] (Supplementary Table 2). These patterns have important implications as to prognosis. Of interest is the fact that although bilirubin does not factor into the R value, it has major prognostic significance as part of the Model for End-Stage Liver Disease score calculation as well as defining Hy's Law.

Although ALT and AST have been the primary biochemical indicators of hepatocellular injury since the 1950s, they are far from being sensitive or specific for DILI.[136] Moreover, these biomarkers do not actually predict injury because they are elevated only after injury has occurred.[17,136,137]

As illustrated by Aithal et al,[111] knowledge of the many mimics of DILI is essential to accurately distinguish between drug and non-drug causes. The injury pattern and the absolute height of liver-associated enzymes (LAEs) play important roles in helping to rule in or rule

Table 4. Drugs Withdrawn, Abandoned, Not Approved, or Given Restrictions in the United States Because of Hepatotoxicity in the Modern Era

Withdrawn	Abandoned	Not approved[a]	Restricted
Iproniazid	Chloroform	Benoxaprofen	Trovafloxacin
Ticrynafen	Cinchophen	Oxmetidine	Telithromycin
Ibufenac	Phenurone	Ebrotidine	Bosentan
Suprofen	Phenindione	Dilevalol	Felbamate
Zoxazolamine	Fenclozic acid	Ajmaline	Tolcapone
Chenodeoxy-cholic acid	Isoxepac	Ximelagatran	
Pemoline	Thorium dioxide	Clometacine	
Oxiphenisatin	Suprofen	Nimesulide	
Troglitazone	Carbutamide	Lumiracoxib	
Bromfenac	Metahexamide		
	Halothane[b]		
	Erythromycin estolate[b]		
	Phenylbutazone		

[a]Available outside of the United States.
[b]Use is limited.

Table 5. Causes of DILI by Drug Class in Various Global Registries

Drug class	Sweden,[79] n = 784	Spain,[78] n = 461	USA,[76] n = 899	Korea,[83] n = 371	Iceland,[82] n = 96	India,[80] n = 313
Antibiotics (%)	27	32	45.4	NS	37	65
Central nervous system (%)	3	17	9.8	NS	7	12
Hypolipidemic (%)	1	5	3.7	NS	3.1	1.6
Other drugs (%)	69	44	25.7	29.5	37	20
Herbals (%)	NS	2	16.1	71.6	16	1.3

NS, not specified.

out possible DILI. Mean values for ALT were 825 IU (about 20× upper limit of normal [ULN]) overall, with mean peak ALT of 1510 for H-cell injury in the updated DILIN series.[76] Mean peak alkaline phosphatase for cholestatic DILI was 682 IU (5–6× ULN). Among Irish patients hospitalized with ALT >1000 IU, non-acetaminophen iDILI accounted for only 16 of 182 cases (8.8%), nearly half of which were due to antituberculous medications.[138] The most common cause for ALT in this range in this series was ischemic hepatitis (61%). Data on mean peak values for other DILI series are given in Supplementary Table 3.

The median peak values for ALT from idiosyncratic drugs causing ALF is in the range of 500 IU,[15] far lower than values seen with acetaminophen injury, which can be among the highest recorded, often in the range of shock liver.[7] Indeed, when ALT or AST is >7500, the differential diagnosis is essentially limited to shock liver, acetaminophen overdose, toxic mushroom, or other chemical poisoning.[7] Acute iDILI would not be expected to approach such towering elevations. Alcoholic liver disease follows a set of rules unlike any other cause: AST > ALT ratio of 2–3:1 with maximal values for AST <300 and ALT <100[7,139]; again, this is not typical of acute iDILI.

Although liver biopsy was once regarded as an important diagnostic tool to identify acute and chronic forms of DILI,[140] recent observations from 249 well-accepted cases of liver injury in the U.S. DILIN concluded that no histologic feature was pathognomonic for DILI.[141] At best, liver biopsy findings may be supportive (Supplementary Table 4) but are most helpful in excluding other possible causes.[73] Certain histologic features may offer prognostic importance.[141]

Diagnosing/Assigning Causality

In the absence of a highly sensitive and specific biomarker, DILI fundamentally remains a diagnosis of exclusion.[59,142] During what I call the Zimmerman-Ishak era of clinicopathologic correlation, most instances of DILI were based on case reports and case series found in the literature as well as the personal knowledge and experience of these 2 seminal observers and thinkers[7,140,143] (Supplementary Tables 4 and 5). Such clinical expertise served them well at the time, but in the current age of newly identified viral causes such as hepatitis E virus[144] and because of the sheer number of potential hepatotoxic agents and confounding causes including underlying liver disease, our ability to confidently diagnose DILI has actually become more difficult.[64,106,145,146]

Roussel Uclaf Causality Assessment Method

An international meeting of hepatic experts, hosted by the French pharmaceutical company Roussel Uclaf, was convened more than a quarter century ago in what was the first formal attempt to create an objective causality assessment tool for DILI.[135] What resulted was a methodology that uses 7 main domains, including onset (latent period) and offset (dechallenge) and, importantly, the response to re-exposure (rechallenge), which served to validate the agents in the original scoring system[147] (Supplementary Table 6).

Although Roussel Uclaf Causality Assessment Method (RUCAM) remains in widespread clinical use (albeit mostly outside of the United States), it is not particularly user-friendly.[64] It was based on the expert consensus opinions of the panel, and scoring requires a fairly high level of expertise and contains numerous questionable elements, a number of omissions (such as not accounting for ultra-short or very long latency and not considering any liver histology), and other deficiencies that reduce its clinical utility[64,148,149] (Supplementary Tables 7 and 8). Because of the advances made in identifying and excluding other causes of acute liver disease in the past 25 years, RUCAM is overdue for reevaluation and revision[64] (Supplementary Table 9). Indeed, owing to its inherent pitfalls, RUCAM is not used as the sole causality assessment method in the DILIN[150] or by many other DILI experts.[64,65] The DILIN approach is to incorporate expert opinion (or what Senior[151] refers to as "medical reasoning") into the elements of RUCAM to arrive at a percentage of likelihood that the drug under question is responsible[150] (Supplementary Table 10).

As the saying goes, it is very difficult to prove a negative, and this was never truer than for establishing

causality for DILI. Lack of data to exclude other causes is a constant source of concern and consternation for both published case reports as well as submissions alleging possible DILI sent to the FDA (eg, MedWatch and FDA Adverse Event Reporting System). Agrawal et al[152] found that the majority of published reports lack many of the important elements that are otherwise needed. In the clinical trial setting, it is easier to regulate the type and number of tests that are performed compared with the office or hospital setting where a high index of suspicion is required.[64,65] In the clinical trial setting, sponsors who want to do everything possible to exonerate their drug under development may opt to obtain every test conceivable to exclude alternatives. In the office setting, however, clinicians often direct their evaluation on the basis of symptoms and the height of the liver tests along with the injury pattern to decide what diagnostic tests would be best, although causality often seems directly proportional to the number of exclusionary tests conducted. Diagnosing DILI in patients with underlying CLD[73,76,106] or in the setting of treating malignant disease[153] or patients with congestive heart failure[154] brings with it an additional set of difficulties, relying heavily on the clinical experience and expertise of the adjudicator. In such settings where the science is still inexact, when to consider a liver biopsy and when and how to exclude acute viral hepatitis or chronic disorders such as fatty liver will require more uniform and validated standards than currently exist.[64,73,105,106]

When it comes to causality of possible liver injury from HDS, the assessment is often made more difficult by the fact that compounds may be adulterated with hepatotoxic contaminants, or many of the ingredients are unclassified or unknown.[77,128,155,156] Perhaps with better manufacturing and regulatory controls in place for HDS and further research, causality will become more accurate.[128,157]

Predicting Drug-induced Livery Injury

The classic host risk factors for DILI are age, gender, underlying liver disease, use of alcohol, and obesity[7,73,139] (Supplementary Table 11). The extent to which they remain independently related to DILI is undergoing reassessment.

Gender

Zimmerman[7] noted that women were more likely to develop DILI compared with men. Whether there is a true gender difference is uncertain, because women tend to be prescribed hepatotoxic medications in higher numbers than men, including minocycline, methyldopa, diclofenac, and nitrofurantoin among others.[73] Nevertheless, most DILI series are predominated by women (Supplementary Table 12).

Age

Although most patients with DILI are adults, children are certainly not immune.[158,159] Hunt et al[160] analyzed the World Health Organization Safety Report Database for age and found an age distribution that mimics clinical experience: 6% in those aged 0–17 years, 62% for those aged 18–64 years, and 32% for patients aged >65 years. Although the RUCAM scoring system awards an extra point for individuals older than the age of 55,[135] this age cutoff was probably arbitrary and is discounted by most experts.[64] In the Vigibase registry, only about one-third of DILI cases were reported for patients older than the age of 55.[84] Similarly, the mean age for DILI in many of the global registries is below that threshold age[161] (Supplementary Table 12). In the U.S. DILIN, only about 1 in 6 cases involved patients aged >65 years.[76] However, those older than the age of 65 had a higher proportion of cholestatic injury (36% versus 21%), although the severity of injury was lower among this older age group.[76] Similarly, older patients were more likely to present with cholestatic injury in the Spanish series,[162] which may be more a function of the drugs they received (ie, a higher proportion of antibiotics, which as a class are known to cause cholestasis) rather than any biological basis of age alone.[76]

Certain drugs do appear to have a propensity to cause injury in an age-dependent fashion, eg, INH, Augmentin, and nitrofurantoin.[7,161] In addition, although it is well-known that certain metabolic processes may be impaired with increasing age,[163] the risk of DILI for most agents does not appear to increase with age alone.[161]

Pharmacologic Properties and Drug-induced Liver Injury

Among non-host–related risk factors for DILI, the daily dose, extent of hepatic metabolism, and degree of lipophilicity may be as or more important than age or gender.[164–166] Traditionally, DILI has been divided into those agents causing predictable (dose-dependent, intrinsic) hepatotoxicity and those that are unpredictable (dose-independent, idiosyncratic) hepatotoxins.[7] This has proved to be an oversimplification because it is now better understood that all DILI is the result of exposure to a minimal threshold dose. Uetrecht et al[87,88] make a strong case for this being at least 10 mg, and others have demonstrated that daily doses of 50–100 mg are responsible for the majority of instances of DILI.[167,168] The Spanish registry noted that >2/3 of drugs causing DILI were prescribed in doses above 50 mg.[167] A high degree of hepatic metabolism (>50%) also correlated with an increased risk of DILI, but not necessarily with greater severity.[165,168]

Taking the dose and degree of hepatic metabolism one step further, Chen et al[33] devised a "Rule-of-Two" that found drugs with high lipophilicity given in doses

exceeding 100 mg were more likely to be hepatotoxic. The Rule-of-Two accurately predicted the liver injury seen with 14 of 15 drugs that had been withdrawn for hepatotoxicity (with the remaining drug given a warning), and it was also able to predict the hepatotoxic component of multidrug regimens. Working with a set of 70 compounds with clear evidence of hepatotoxicity, Chen et al[34] showed that the accuracy of the Rule-of-Two in predicting DILI was increased by 10%, and the number of drugs requiring additional experimental assessment was reduced by approximately 20% compared with high-content screening methodologies alone. In an attempt to refine the relationship between hepatic metabolism and daily dose, Yu et al,[169] utilizing the Liver Toxicity Knowledge Base Benchmark Dataset of >250 drugs, evaluated the role of P450 enzymes and DILI. They found that the only combination of pharmacologic factors predicting a higher likelihood of DILI was an agent being a substrate of P450 metabolism and given in a high daily dose. Interestingly, high lipophilicity was not a significant factor in their multivariate logistic regression analysis, suggesting that the initial 'rule of two'[33] may have to be redefined.

"Omics" and Drug-induced Liver Injury

The fields of pharmacogenomics, metabolomics, proteomics, and others have revolutionized the field of drug discovery and are making substantial progress into identifying new predictive biomarkers and genetic risk factors for DILI.[59,91,95,142,164,170]

Biomarkers

By using banked sera collected from patients in the DILIN, Bell et al[60] found that proteomic profiling identified several compounds such as apolipoprotein E that hold potential promise as biomarkers, although none has yet come to fruition as a true predictor of individual agents causing iDILI.[59] In contrast, certain biomarkers of hepatocyte necrosis and apoptosis (such as microRNA-122, high mobility group box-1, and keratin 18) appear useful in identifying those adults with acute acetaminophen toxicity who present with normal liver biochemistries who may go on to develop more severe injury.[170–173] Similar findings have also been shown in children.[174] These particular biomarkers, alone or in combination, may become useful adjuncts to the acetaminophen toxicity nomogram to predict which individuals will require treatment,[172,175] although Senior[151] cautions that the ability of such biomarkers to establish causality remains an ongoing concern.

Pharmacogenetics

The current excitement and enthusiasm for personalized medicine have also permeated the field of hepatotoxicity in the form of pre-prescription pharmacogenetic testing to predict DILI. Genome-wide association study analyses have identified HLA and cytochrome phenotypic alterations that can be associated with an increased risk of DILI.[54,55] However, to date, few drugs have had verified associations with risk alleles uncovered from HLA genotyping, and they appear to be largely drug-specific[99–101,104] (Supplementary Table 13). As a case in point, among a recent genome-wide association study conducted on 783 patients of European ancestry from the U.S. DILIN and 3 international registries representing more than 200 implicated drugs, no significant genome-wide associations were seen apart from those for flucloxacillin and amoxicillin-clavulanate.[99] Also, the current state of the science is tempered by the reality that such testing, while having a high negative predictive value, has a relatively low positive predictive value.[55,99,104]

Drugs causing hepatocelluar injury did show a trend toward an association in the vicinity of STAT4 (signal transducer and activator), suggesting a causal role of the innate immune system.[100] However, with a risk of about 1 in 500 for individuals carrying the HLA-B*5701 genotype for flucloxacillin DILI, clinicians in practice have not yet embraced such testing, even with a negative predictive value of 88%.[55,100,104] To date, the only drug for which HLA testing is recommended by FDA before initiation of treatment is abacavir. For the 4%–5% of human immunodeficiency virus positive patients who harbor HLA-B*5701, withholding the drug has led to a reduction in the number of severe hypersensitivity skin reactions, some of which are associated with DILI.[176] For other drugs in which genetic predictors have been identified, no formal recommendations have emerged as to whether these medications should be withheld,[17,55,59,73,100] although a case can probably be made for adjusting the dose of antituberculous medications on the basis of acetylator status.[104,177]

Chronic Liver Disease and Drug-induced Liver Injury

Many clinicians are appropriately reticent to prescribe medications that are potentially hepatotoxic to individuals with underlying liver disease. The only examples that appear to have a defined increased risk of DILI in CLD are the antituberculous medications and some antiretroviral medications in patients with chronic hepatitis B or C.[178] In addition, leflunomide, especially in combination with methotrexate, appears to be at higher risk of causing DILI.[179,180]

Zimmerman[7] remarked that CLD by itself was not a significant risk factor for the vast majority of drugs being taken but provided a caveat that if acute hepatic injury developed in a patient with significant CLD, the consequences could be dire. Although many medications carry recommendations to reduce the dose in patients with

hepatic impairment,[181,182] it is unclear whether that strategy is, in fact, protective against acute DILI.[183] The vast majority of medications can be taken safely by patients with cirrhosis without added risk of acute DILI.[178,183,184] It often comes as a surprise to many patients and clinicians alike that acetaminophen taken in doses ≤2 g a day is considered a relatively safe alternative to nonsteroidal anti-inflammatory drugs, even in the face of cirrhosis.[183,185,186] Nevertheless, a study by Watkins et al[187] is an important reminder that acetaminophen, taken in the maximum therapeutic dose of 4 g daily (with or without narcotic analgesics) for up to 14 days by healthy male and female volunteers, caused elevations in ALT >3× ULN in 39%, with 19% experiencing ALT >5× ULN. All rises in ALT were observed after at least 3 days of treatment, with the highest recorded ALT being 636 IU/L (16× ULN). Despite these marked elevations, all subjects remained asymptomatic, and the ALT values declined to <3× ULN within a median of 6.5 days. The combination of acetaminophen with a narcotic did not increase the risk of ALT elevations compared with acetaminophen alone. However, lower doses of acetaminophen were not studied, leaving open the risk of exceeding 2 or 3 g daily for 4 days or longer, especially in patients with CLD.

One of 10 patients in the DILIN registry had preexisting CLD (mostly nonalcoholic fatty liver disease or hepatitis C).[76] In general, they had similar clinical features and demographics to patients without CLD, and there were no significant differences in the classes of agents causing DILI, suggesting that CLD in general did not increase the risk of DILI. Among the 5 leading causes of injury in DILIN (antimicrobials, herbals, cardiovascular drugs, antineoplastic agents, and central nervous system–acting drugs) (Table 5, Supplementary Table 1), there were no significant differences between patients with and without CLD. The one exception was azithromycin, which was found to be a statistically higher cause of DILI in the CLD group (6.7% vs 1.5%).[76]

Three-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) are one of the best studied drug classes in CLD and appear safe in this setting.[188] Both retrospective analyses and prospective clinical trials have demonstrated the hepatic safety of these agents in this setting.[189–191] In particular, a prospective, randomized, placebo-controlled trial of high-dose pravastatin was designed to assess safety and efficacy in 326 hypercholesterolemic patients with mostly nonalcoholic fatty liver disease or hepatitis C virus who had baseline elevations of ALT up to 5× ULN.[190] The safety end point of a doubling of the baseline ALT occurred less frequently in the pravastatin group compared with the placebo recipients at all time points, suggesting that lowering of lipids also had a salutatory effect on fatty liver and ALT values. These data, coupled with finding that statins may reduce the risk of hepatocellular carcinoma and other malignancies, have helped remove most concerns about prescribing statins in CLD.[188,189,192–194]

Prognosis/Natural History of Drug-induced Liver Injury

Hy's Law

The late Hyman Zimmerman was quoted as saying as early as 1978 that drugs causing acute hepatocellular injury with jaundice were associated with a case-fatality rate of 10% or higher.[23,124,137,195,196] The agents involved were many of the classic hepatotoxins of the times in an era largely predating ALT monitoring and liver transplantation.[7,124] Such cases often involved dramatic elevations in aminotransferases and bilirubin. Zimmerman recognized that this particular combination of liver injury biomarkers reflected a degree of hepatic functional impairment that could be life-threatening.[137] In what was later affectionately referred to as "Hy's Rule" and later "Hy's Law" by Robert Temple at FDA,[23,137,195,197] this relatively humble biochemical observation has evolved into one of the most important clinical measures of hepatic safety with significant regulatory implications.[20,23,198]

Focusing their attention on the drug development process and clinical trial testing, Robert Temple, along with John Senior and others at FDA, modified these biochemical parameters so that hepatotoxicity of drugs under study could be identified well before crossing the threshold of irreversible liver failure. The regulatory definition of this modified Hy's Law,[20,23,137,196] as it currently stands, consists of ALT/AST >3× ULN in combination with total bilirubin >2× ULN in the absence of cholestatic injury (alkaline phosphatase <2× ULN) and no other cause identified.[17,19,73,198] It can be represented graphically in an Evaluation of Drug-Induced Serious Hepatotoxicity plot (Supplementary Figure 1). This definition, which some refer to as "Hy's Law criteria," implying that causality assessment is still required,[196] is an essential part of the stopping rules as set forth in FDA guidance to industry on preventing hepatotoxicity in the preapproval development process.[199] Even a single patient adjudicated as a possible Hy's Law case can be grounds for suspending further clinical testing and even abandoning development of the drug in question entirely.[199]

Although Hy's Law was never specifically validated in a clinical trial during his lifetime,[137] the observation has stood the test of time. A number of studies have recorded a combined rate of death or need for liver transplant of approximately 10% (Table 6).[76,78,79,200] In India, where liver transplant was not available, mortality rates are even higher.[80,201] Among patients with CLD, the DILIN series reported higher mortality in this subgroup (16% versus 5.2%), verifying Zimmerman's axiom that if acute injury occurred in a patient with CLD, especially cirrhosis, the outcome would predictably be worse.[7,76]

By using a database of oncology trials, Parks et al[202] suggested that threshold elevations be raised to ALT

Table 6. Hy's Law in iDILI Cases in Global Registries

Country	Sweden[79]	Spain[78]	USA[76]	India[80]
Years	1970–2004	1994–2004	2004–2013	1997–2008
No. of patients	784	446	899	313
Study type	National registry	Prospective 32 centers	Prospective 10 centers	Retrospective single center
Hepatocellular injury	52	58	54	NS
Mixed/cholestatic (%)	22/26	22/20	23/23	
Age (*y*)	58	53	49	39.3
Female (%)	58	49	59	42
Hospitalized (%)	NS	53	59	100
Overall death/LT (%)	9.2	7.1 (5.4/1.7)	10.2 (6.2/4)	17.3[a]
Hepatocellular DILI (%)	12.7	7/3	5.4/6.2	Anti-TB drugs, 21.5
Cholestatic DILI (%)	7.8	5/1	2.9	Other drugs, 11.4
Mixed DILI (%)	2.4	2/0	0	
Chronic DILI (%)	NS	10.3	16.6	NS

LT, liver transplant; NS, not stated; TB, tuberculosis.
[a]LT not available.

6.9× the baseline value and bilirubin 6.5× baseline to prevent premature discontinuation of a potential valuable therapy in patients with and without hepatic metastases. Robles-Diaz et al[203] proposed a new composite algorithm to predict ALF. By using AST >17.3× ULN, total bilirubin >6.6× ULN, and AST:ALT ratio >1.5, they found a specificity of 82% and a sensitivity of 80%. Two-thirds of these patients were jaundiced, and more than 50% were hospitalized, reflecting the advanced nature of the liver injury. Whether such revised definitions become part of clinical or regulatory practice is yet to be determined.[198]

Although Zimmerman downplayed cholestatic injury in his prognostic modeling, particularly as cholestatic hepatotoxins rarely caused acute liver failure in his experience,[7,204] the current DILI registries do suggest that cholestatic drugs can also be associated with significant morbidity and mortality (Table 6).[76,78,79,200]

Acute Drug-induced Liver Injury Becoming Chronic

It has long been axiomatic that if a drug causing acute DILI is discontinued, the injury is expected to resolve.[205] Hepatocellular injury generally does so within several weeks, whereas cholestatic injury can take up to several months.[78,206] For a select number of drugs (many of which were antimicrobials causing acute cholestasis), injury persisted even after the drug was discontinued.[206] Many of these cases mimicked primary biliary cirrhosis, and in rare instances, vanishing bile duct syndrome led to biliary cirrhosis and portal hypertension.[207–209] In contrast, drugs given short-term and causing acute hepatocellular injury have only rarely been implicated in chronic DILI after the medication is stopped.[206] Drugs that are administered chronically (eg, nitrofurantoin, minocycline, methyldopa) may cause insidious injury (eg, autoimmune hepatitis), but it is usually self-limited, resolving after the drug is stopped or after a course of immunosuppressive therapy.[210,211] Liver biopsy may be helpful in differentiating idiopathic from drug-induced autoimmune hepatitis in such instances (Supplementary Table 4).[212]

An important aspect of the prospective nature of the U.S. DILIN is the mandatory follow-up of patients to define which agents causing acute DILI may become chronic.[76,200] The definition of chronic DILI was arbitrarily set as persistent abnormalities 6 months after the acute event, and this may be too short a duration, because slow-to-resolve DILI may be confused with true chronic injury.[198] To this end, the U.S. DILIN is prospectively following acute DILI cases out to at least 24 months.[213] Current data indicate that nearly 19% of cases have persistently elevated LAEs at 6 months,[200] and about 75% are still elevated at 12 months.[213] The majority of these "persisters" are patients who took agents causing cholestatic injury, as has been the case historically.[206] Histologic findings in DILIN suggested that outcomes were worse in patients whose histology showed greater degrees of necrosis, microvesicular steatosis, higher stages of fibrosis, and ductular reactions. In contrast, milder injury was associated with the presence of granulomas and eosinophilic infiltrates.[141] Long-term follow-up in Sweden found that among 685 patients evaluated after a median time of 10 years, chronic injury was rare. Only 5 patients (0.73%) had cryptogenic cirrhosis for which DILI might have been responsible.[214]

Preventing Drug-induced Liver Injury

Bjornson et al[181] note that for most drugs that can cause liver injury, product labels call for dose reduction if liver disease is present and often carry a warning that they should be used cautiously in the setting of CLD. However, there is little if any information to currently support the notion that a lower dose would in fact lead to a decreased risk of hepatic injury.[183]

Liver-associated Biochemistry Monitoring

LAE monitoring was born out of the observation that if a drug is stopped before crossing the threshold of ALF, recovery can be expected.[7,205] Although dozens of drugs have had ALT monitoring recommended,[139] it remains largely unproven that the time, expense, and inconvenience of performing such monitoring is actually effective. Even in instances where a drug is known to cause life-threatening hepatotoxicity and under the threat of several regulatory actions to mandate monitoring, the recommendation has fallen short. Such was the case with troglitazone, where fewer than 5% of patients were still being monitored appropriately after 3 months.[215] One of the only examples where ALT monitoring has been considered to be effective is bosentan.[216] But even here under one of the most restrictive and stringent risk evaluation and mitigation strategies, adherence has been suboptimal.[216] Pre-prescription testing for CYP2C9 polymorphisms that convey an increased risk of DILI from bosentan[217,218] might prove to be a more effective method to prevent DILI than ALT monitoring,[219] but this presupposes that such pharmacogenetic screening is accurate.[220] Whether the availability of a finger stick test for ALT, akin to home glucose testing, would change attitudes or practice patterns is unknown but remains close to reality.[221,222] Ultimately, it is expected that all biochemical monitoring will be supplanted by a form of predictive testing.[219]

Recommendations to monitor INH in patients without liver disease call for the self-reporting of hepatitis-related symptoms without routine ALT testing, because the majority of individuals taking INH worldwide do so safely.[223] Nevertheless, the success of this form of monitoring may be in the eye of the beholder, because INH remains a major cause of severe DILI and DI-ALF worldwide.[16,76,80,201] An analysis of the DILIN registry not surprisingly found that adherence to the American Thoracic Society guidelines was poor in patients who developed acute DILI, with 55% continuing INH for more than 7 days despite meeting stopping criteria.[224] As these investigators suggested,[224] perhaps the use of a mobile phone text messaging system to remind patients to report symptoms would improve outcomes.[225]

Of particular note, statins were initially given labeling that required regular LAE monitoring, which was based on both animal toxicity findings as well as the clinical trial data.[188] However, compliance with monitoring was very poor.[226] As the hepatic safety of statins grew to be recognized, the stance at FDA changed, and the need for ALT monitoring in patients with normal values at baseline was eventually dropped.[188,227] For patients requiring statins who have CLD, most experts consider ALT monitoring for the first few months to be prudent, because the potential benefits of the drug appear to outweigh the risks.[188]

Desensitization-Rechallenge

Deliberate re-exposure (rechallenge) to the same drug suspected as causing acute iDILI is generally discouraged[73,139,228] for fear of producing an even more severe reaction, including death from ALF.[229–231] For certain life-threatening illness, such as active tuberculosis, where no alternative therapies are available, desensitization-rechallenge strategies have been successfully implemented, whereby the same agents causing DILI can be restarted.[232–235]

The strategy of switching from one drug to another in the same or related class in an attempt to avoid recurrent hepatotoxicity in a patient experiencing iDILI is probably done frequently in clinical practice, but formal studies are lacking. Successful drug substitutions in this setting have been reported for statins,[236] thiazolidinediones,[237] and non-estolate salts of erythromycin.[209] In the case of penicillin, cephalosporins can generally be given safely, although the semisynthetic penicillins have actually been more likely to cause DILI.[238] Similarly, the ketolide, telithromycin, is at least as likely to cause liver injury as macrolides.[238]

Restricting Access to Acetaminophen

Attempts to restrict access to acetaminophen (paracetamol) in certain European countries to as little as 12 g (because 10 g is generally considered the threshold for ALF to occur) initially demonstrated a significant reduction in deaths and liver transplants due to liver failure.[239] In the most recent analysis of the effects of this legislation, a 43% reduction in the number of suicide-related or undetermined deaths involving paracetamol (with or without alcohol) has translated into 765 fewer deaths during the past 11 years.[240] Inadvertent overdoses among adults as well as children remain problematic but should be preventable through better education and improved product labeling.[241,242] Duration of usage is also an important consideration, as demonstrated by Watkins et al,[187] where 4 g taken daily for more than 3 days can lead to significant elevations in ALT, even among healthy persons.

Treating Drug-induced Liver Injury

Lagging behind all of the advances in the detection, diagnosis, and prevention of DILI is our ability to treat acute DILI.[6,73,205] The cardinal rule to limit injury is to stop the suspected offending agent as soon as possible.[7,73] In some cases this means discontinuing a drug that is efficacious, and in situations where there are no alternative agents, the patient may be deprived of a beneficial medication, especially if causality is in doubt.[111] Some patients have received ursodiol or steroids in cases of cholestatic DILI, although such treatment has been met with only anecdotal success.[70,73,205,243]

N-acetylcysteine has been available for decades and is extremely effective at managing and preventing acute injury to acetaminophen overdose.[242,244] Oral and intravenous formulations appear equally effective,[245] but identifying patients at risk for hypersensitivity reactions to N-acetylcysteine is essential.[246] Few, if any, specific antidotes are available to treat acute hepatotoxicity from other agents. The use of N-acetylcysteine for non-acetaminophen DI-ALF appears to have only limited utility in adults before the development of hepatic coma[71] and is not helpful in children.[72] Carnitine supplementation may ameliorate injury from valproic acid,[247] as might folic acid to reduce methotrexate toxicity.[248] An enterohepatic washout regimen of cholestyramine is recommended to hasten clearance of the drug in patients with suspected hepatic (or other organ) injury from leflunamide.[249]

The use of liver assist devices such as molecular adsorbent recirculating systems or plasma exchange has proven effective as a bridge to transplant but remains largely investigational.[68,69,250–252] The role of nanotechnology to deliver hepatoprotective agents to the liver promises for the future.[67] The benefits of hepatic cytoprotection by using silymarin (milk thistle) and other potential nutriceuticals in acute DILI is largely anecdotal[253] but deserves further study.

Liver transplantation remains an important rescue procedure in the case of irreversible ALF but is limited by its availability.[16,254] As the saying goes, the best treatment is prevention, and this is certainly true when it comes to DILI.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.06.017.

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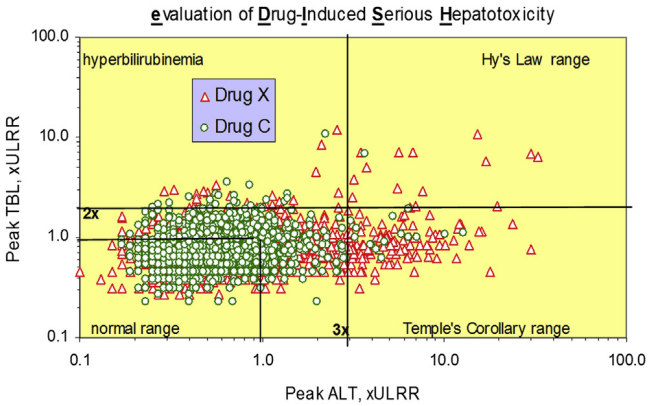
The author discloses no conflicts.



Supplementary Figure 1. Evaluation of Drug-Induced Serious Hepatotoxicity plot. Graphic representation of ALT and total bilirubin (TLB) values from clinical trial comparing 2 drugs in this theoretical example. Subjects with ALT $<3\times$ ULN and TLB $<2\times$ ULN are shown in *left lower* (normal) quadrant of the plot. Subjects with ALT $>3\times$ ULN and TLB $>2\times$ ULN are displayed in the Hy's Law (*right upper*) quadrant, implying the possibility that DI-ALF might develop. Subjects with ALT $>3\times$ ULN and TLB $<2\times$ ULN are displayed in the Temple's corollary (*right lower*) quadrant, implying that serious DILI is still possible. Subjects with possible cholestatic injury, Gilbert's syndrome, or hemolysis are seen in *left upper* (hyperbilirubinemia) quadrant. Evaluation of Drug-Induced Serious Hepatotoxicity plots can be devised that directly link each individual point to a narrative or other patient information to assist in the adjudication process to determine causality.[32]

Supplementary Table 1. Most Common Individual Causes of iDILI in Various Global Registries

U.S. DILIN,[76] n = 899	Spain,[78] n = 446	Sweden,[79] n = 784	Iceland,[82] n = 96	India,[80] n = 313
Amoxicillin-clavulanate 10%	Amoxicillin-clavulanate 13.2%	Flucloxacillin 16.5%	Amoxicillin-clavulanate 22.9%	INH + anti-TB 57.8%
INH 5.3%	INH + anti-TB 6.9%	Erythromycin 5.4%	Diclofenac 6.3%	Phenytoin 6.7%
Nitrofurantoin 4.7%	Ebrotidine 4.9%	Disulfiram 3.4%	Nitrofurantoin 4.2%	Dapsone 5.4%
SMX-TMP 3.4%	Ibuprofen 4%	TMP-SMX 2.7%	Infliximab 4.2%	Olanzapine 5.4%
Minocycline 3.1%	Flutamide 3.8%	Diclofenac 2.6%	Azathioprine 4.2%	Carbamazine 2.9%
Cefazolin 2.2%	Ticlopidine 2.9%	Carbamazepine 2.2%	Isotretinoin 3.1%	Cotrimoxazole 2.2%
Azithromycin 2%	Diclofenac 2.7%	Halothane 1.9%	Atorvastatin 2.1%	Atorvastatin 1.6%
Ciprofloxacin 1.8%	Nimesulide 2%	Naproxen 1.4%	Doxycycline 2.1%	Leflunamide 1.3%
Levofloxacin 1.4%	Carbamazepine 1.8%	Ranitidine 1.3%		Ayurvedic 1.3%
Diclofenac 1.3%	Bentazepam 1.6%	Enalapril 1%		Methotrexate 1%

SMX, sulfamethoxazole; TB, tuberculosis; TMP, trimethoprim.

Supplementary Table 2. Calculating R Values

Calculation of R value
ALT/AST value divided by its ULN = fold elevation ÷ fold elevation above ULN for alkaline phosphatase
Definitions
Hepatocellular injury = R > 5
Cholestatic injury = R < 2
Mixed injury = R >2 <5

Supplementary Table 3. Mean and Peak LAE Values From Various Causes of Acute DILI

	Registry						
					USALFSG[15]		
	U.S. DILIN[76]	Sweden[79]	Spain[78]	India[80]	APAP	iDILI	USALFSG iDILI[16]
Mean AST (*IU*)	—	7.2 × ULN	—	405	—		561.15
Mean ALT (*IU*)	825	12.5 × ULN	—	394	3773	639.5	609.1
Mean AP (*IU*)	288	2.1 × ULN	—	311			165.3
Mean bilirubin (*mg/dL*)	6.7	6.2 × ULN	—	8.5	4.3	19.8	19.45
Peak ALT in H-cell DILI (mean)	1510	34.3 × ULN	(31×)[a]	—	—	—	—
Peak AP in cholestatic (mean)	339	6 × ULN	(5.2) 32.7×	—	—	—	—
Peak ALT in ALF	—	56 × ULN[b]	(30.4×)	537.1[c]	—	—	2013.5
Peak AST in ALF	—	59 × ULN[b]	—	661.7[c]	—	—	1418.5
Peak bilirubin in ALF	—	25.3 × ULN[b]	(16.9×)	19.2[c]	—	—	29.8

ALFSG, Acute Liver Failure Study Group; AP, alkaline phosphate; APAP, acetaminophen; LT, liver transplant.
[a]x = fold above normal.
[b]In fatal or LT cases.
[c]In non-survivors (LT not available).

Supplementary Table 4. Histologic Findings Suggesting Possible DILI

Finding	Drug examples
I. Steatosis	
• Microvesicular steatosis	Valproate, tetracycline, salicylates, didanosine
• Macrovesicular steatosis	Tamoxifen, methotrexate, ethanol, lopitamide
• Phospholipidosis	Amiodarone
II. Necroinflammation	
• Autoimmune hepatitis–like	Minocycline, nitrofurantoin, methyldopa
• Acute viral hepatitis–like	INH, sulfonamides, diclofenac
• Mononucleosis-like	Phenytoin, para-aminosalicylate, dapsone
III. Cholestasis	
• Intrahepatic (bland) cholestasis	C-17 alkylated anabolic, contraceptive steroids, TPN
• PBC-like ductopenia	Chlorpromazine, thiabendazole, haloperidol, imipramine
• PSC-like biliary sclerosis	Floxuridine via hepatic artery infusion
IV. Vascular	
• Peliosis	Anabolic steroids, vinyl chloride
• Sinusoidal dilatation	Contraceptive steroids
• Sinusoidal obstruction syndrome	Cyclophosphamide, pyrrolizidine alkaloids
• Nodular regenerative hyperplasia	Azathioprine, 6-thioguanine
• Hepatoportal sclerosis	Anti-neoplastic agents, arsenicals
V. Granulomas	
• Fibrin-ring type	Allopurinol
• Multinucleated giant cell type	Phenylbutazone
• With associated cholangitis	Chlorpromazine, methyldopa, allopurinol
• With associated vasculitis	Sulfonamide, phenytoin, glibenclamide
VI. Neoplastic	
• Hepatic adenoma	Contraceptive steroids
• Angiosarcoma	Androgenic steroids, vinyl chloride, thorium dioxide
• Hepatocellular carcinoma	Androgens, estrogens, arsenicals, methyltestosterone
VII. Miscellaneous	
• Mallory-Denk bodies	Amiodarone
• Portal neutrophils and intracellular cholestasis	Favors DI-AIH meeting criteria for AIH

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TPN, total parenteral nutrition.

Supplementary Table 5. Classic Clinical Syndromes Associated With Acute DILI

- Acute viral hepatitis–like: eg, isoniazid: absence of hypersensitivity symptoms; present with malaise, fatigue, anorexia, nausea, vomiting, right upper quadrant pain
- Hypersensitivity syndrome: fever, rash, and/or eosinophilia seen in 25%–30% of DILI cases, usually with short latency and prompt rechallenge response (eg, amoxicillin-clavulanate, phenytoin, carbamazepine, sulfamethoxazole-trimethoprim, halothane)
- Sulfone syndrome: eg, dapsone: fever, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis, eosinophilia, hemolytic anemia, methemoglobinemia
- Pseudomononucleosis syndrome: eg, phenytoin, dapsone, sulfonamides: hypersensitivity syndrome with atypical lymphocytosis, lymphadenopathy, and splenomegaly
- DILI associated with severe skin injury: Stevens-Johnson syndrome, toxic epidermal necrolysis, eg, beta-lactam antibiotics, allopurinol, carbamazepine
- Autoimmune hepatitis associated with positive autoantibodies: eg, nitrofurantoin, minocycline, methyldopa
- Immune-mediated colitis with autoimmune hepatitis: eg, ipilimumab
- Acute cholecystitis–like: eg, erythromycin estolate
- Reye syndrome–like: eg, valproic acid: hepatocellular injury, acidosis, hyperammonemia, encephalopathy, abdominal pain, nausea, vomiting, paradoxical worsening of seizure activity, microvesicular steatosis on biopsy

Supplementary Table 6. RUCAM Assessment Criteria for Awarding (or Subtracting) Points

1. Time to onset (latency)
   a. Suggestive
   b. Compatible from start of the drug or from cessation of the drug
2. Course (response to discontinuation; de-challenge)
   a. Highly suggestive
   b. Suggestive
   c. Compatible
   d. Inconclusive
   e. Against the drug
   f. Considered inconclusive in all situations if the drug is continued
3. Risk factors
   a. Presence or absence of ethanol (for hepatocellular injury)
   b. Ethanol or pregnancy (for cholestatic injury)
   c. Age ($\leq$55 or $\geq$55 y)
4. Concomitant medications
   a. With evidence of known hepatotoxic potential
   b. Without known hepatotoxic potential
5. Search for non-drug causes
   a. Six group I causes (viral hepatitis A, B, C; biliary obstruction; alcoholism; acute recent hypotension)
   b. Two group II causes (complications of underlying disease, other viral illnesses, eg, cytomegalovirus, Epstein-Barr virus, herpes simplex virus)
6. Previous information on hepatotoxicity of the drug
   a. Labeled reaction
   b. Published reaction
   c. Unknown
7. Response to readministration (re-challenge)
   a. Positive
   b. Compatible
   c. Negative
   d. Not done or not interpretable

Supplementary Table 7. Pitfalls and Ambiguities in RUCAM Scoring

RUCAM criteria	The science	The art
Age >55 y (awarded extra point)	Age in most registries <55 y	Older patients have more cholestatic DILI
Alcohol use (awarded extra point)	Relatively few drugs affected (eg, INH, methotrexate)	Amount of alcohol undefined
Pregnancy (awarded extra point in cholestatic DILI)	Most cases of acute hepatitis pregnancy due to viral hepatitis	Unclear whether pregnancy is a true risk factor for DILI
Latency >5 days <90 days awarded the most points	Majority of iDILI cases occur within 2 weeks to 6 months	Many drugs with ultrashort latency periods or those occurring after 90 days receive fewer points
Only reactions occurring ≤15 days (for H-cell injury) or ≤30 days (for cholestatic injury) after drug is stopped receive points	Several drugs cause delayed DILI up to several weeks after discontinuation, eg, amoxicillin-clavulanate, telithromycin	Delayed DILI after 15–30 days should receive points if applicable
Dechallenge criteria	Hepatocellular DILI improves more quickly than cholestatic reactions	Times to decrease from peak values are arbitrary
Eight non-drug exclusion categories	Hepatitis C virus, hepatitis E virus have been found in post-causation analyses and should routinely be tested in cases of acute hepatocellular DILI	Impossible to prove a negative: newer DILI mimics (eg, hepatitis E virus) were not initially taken into account
Hepatotoxicity in the product label scores higher than published reports	LiverTox offers the most complete information on >650 causes of DILI	Product labeling of hepatotoxicity often not fully adjudicated
Rechallenge formed the basis of causality	Rarely performed today because of the risk of causing a more severe reaction	Doubling of ALT is an arbitrary criterion
Liver histology not included	Most useful in diagnosing autoimmune hepatitis, drugs causing microvesicular steatosis and excluding non-drug causes	Biopsy information can be factored into the overall assessment
Dechallenge criteria only based on drugs that are discontinued	Injury from many drugs that are continued in the setting of early hepatotoxicity does not progress	RUCAM does not allow for a diagnosis of drug "adaptation" that may be considered related to the agent in question

Supplementary Table 8. Controversies in Assigning Causality for DILI That Require Expert Interpretation

1. Diagnosing acute DILI in the setting of CLD or in patients with liver metastases
2. Diagnosing DILI that occurs after a drug has been discontinued
3. Determining when to initiate a work-up for alternative causes and how extensive the evaluation should be on the basis of the injury pattern and height and ratio of the LAEs
4. Interpreting histologic findings (if available)
5. Differentiating alcoholic liver disease from DILI
6. Determining the influence of concomitant medications, drug-drug interactions, and polypharmacy
7. Differentiating DILI from acute exacerbation of viral hepatitis (eg, B or C)
8. Determining the influence of passage of a gallstone, biliary strictures, muscle injury, etc on LAEs
9. Interpreting fluctuations in aminotransferase levels and ALT:AST ratios
10. Taking the absolute height of ALT and AST into consideration and how to best interpret increases above elevated baseline values
11. Interpreting atypical or negative rechallenge responses
12. Interpreting atypical dechallenge responses that may not conform to RUCAM criteria
13. Assessing herbal and dietary supplement–suspected DILI
14. Attributing tolerance/adaptation to the drug in question when it is continued in the face of early injury

Supplementary Table 9. Possible Modifications of RUCAM to Improve Its Accuracy

1. Compatible hepatic histology
2. Interpreting the risk of underlying liver disease
3. Increased DILI risk associated with higher daily drug doses
4. Increased DILI risk of higher lipophilicity and drug dose ("Rule of Two") or greater degrees of hepatic metabolism
5. Presence of DILI biomarkers from proteomic or cytokine analytes
6. Presence (or absence) of hypersensitivity hallmarks (fever, rash, eosinophilia)
7. Human immunodeficiency virus status
8. Presence or absence of pharmacogenetic susceptibility factors (eg, HLA, CYP polymorphisms)
9. Presence of blood levels of the suspected drug
10. Positive (or negative) lymphocyte transformation tests (where available)[a]
11. Is the suspect drug listed in LiverTox?
12. Fractionation of total bilirubin (into direct and indirect) to exclude Gilbert's syndrome, hemolysis, etc
13. Fractionation of serum alkaline phosphatase to confirm hepatic origin
14. Use of standardized minimal elevations of LAEs to define severe DILI in patients with CLD
15. Availability of long-term follow-up information to assess outcomes
16. Development of a computerized point scoring system to avoid ambiguities

[a]Not available in the United States or approved by FDA.

Supplementary Table 10. DILIN Scoring Criteria

Causal relationship	Percentage of likelihood	Definition
Unlikely	<25	Clear evidence that an etiology other than the drug is responsible
Possible	25–49	Evidence for the drug is present but equivocal
Probable	50–75	Preponderance of the evidence links the drug to the injury
Highly likely	75–95	Evidence for the drug causing injury is clear and convincing but not definite
Definite	>95	Evidence of the drug being causal is beyond any reasonable doubt

Supplementary Table 11. Non-Drug Risk Factors for DILI

Factor	Examples of drugs at risk
Older age	Anti-tuberculous agents, erythromycin, halothane, nitrofurantoin, flucloxacillin, amoxicillin/clavulanate (cholestatic form)
Children	Salicylates (Reye syndrome), valproate
Obesity	Methotrexate, halothane
Fasting/malnutrition	Acetaminophen
Female gender	Diclofenac, sulindac, halothane, flucloxacillin, INH, nitrofurantoin, chlorpromazine, erythromycin
Chronic alcoholism	Acetaminophen, methotrexate, INH, halothane
Human immunodeficiency virus infection	Trimethoprim-sulfamethoxazole
Coinfection with hepatitis B virus or hepatitis C virus	Highly active antiretroviral therapy, antituberculous drugs

Supplementary Table 12. Age and Gender of DILI Cases in Global Registries

Country	Type of DILI	Mean age (*y*)	Age range (*y*)	% Female
Spain	Acute DILI	52	13–88	48
Sweden	Acute DILI	58	42–74	58
United States	Acute DILI	49 (16.6%)[a]		59
India	Acute DILI	39.3	12–84	42
Japan	Acute DILI	60 (46.5%)[a]	11–91	56
Korea	Acute DILI	49	16–79	63.3
United States	Acetaminophen ALF	36	19–76	79
United States	Non-acetaminophen ALF	43.8	17–73	7.7

[a]Percentage age >65 y.

Supplementary Table 13. Genetic Risk Factors for DILI[55]

Drug	Risk allele	Odds ratio
Antituberculous agents (INH, rifampicin, pyrazinamide)	HLA-DQB1*02:01	1.9
	HLA-DQA1*01:02	0.2[a]
Amoxicillin-clavulanate	DRB1*15:01 DQB1*06:02	2.3–10
	DRB1*07	0.18[a]
Flucloxacillin	DRB1*07:01-DQB1*03:03	7
	DRB1*15	[a]
Lapatinib	DRB!*07:01-DQA1*02:01	2.6–9
Lumiracoxib	DRB1*15:01-DQB1*06:02-DRB5*01:01-DQA1*01:02	5
Nevirapine	DRB1*01:02	4.72
Ximelagatran	DRB1*07-DQA1*02	4.4

[a]Risk decreased.